Remarks

Claims 1-4, 6-15, 18-19, 20 and 50 are canceled herein. New claims 67-77 are added herein. Thus, after entry of this amendment, claims 37-38, 40-41, 52-57 and 61-77 are pending. Applicants believe no new matter is added herein.

Rejection Under 35 USC § 112, First Paragraph

Claims 37-38, 40-41, 52-57 and 61-66 were rejected under 35 U.S.C. 112, first paragraph, as allegedly not being enabled by the specification. Applicants respectfully disagree with the rejection as it may be applied to the claims as amended, and as it may be applied to new claims 69-77.

The Office action acknowledges that the specification is "enabling for the method recited in the claims, wherein the oligodeoxynucleotide consists of the nucleic acid sequence set forth as SEQ ID NO: 200....: Solely to advance prosecution, claim 37 has been amended to be directed to a method of enhancing the immunogenicity of a vaccine against *Bacillus anthracis* in a subject, comprising administering to the subject a therapeutically effective amount of an oligodeoxynucleotide **consisting of** the nucleic acid sequence set forth as SEQ ID NO: 200 in combination with the vaccine against *Bacillus anthracis*. Thus, claim 37 as amended is acknowledged in the Office action to be fully enabled by the specification, as is in condition for allowance. Claims 38, 40-41, 52-56 and 67-68 depend from, and further limit the subject matter of, claim 37. Thus, claims 38, 40-41, 52-56 and 67-68 are also in condition for allowance.

Applicants respectfully disagree with the rejection as applied to claims 57 and 61-66, and as may be applied to new claims 69-77.

The Office action acknowledges that results have been provided with an oligonucleotide that has the nucleotide sequence set forth as SEQ ID NO; 200 and a *Bacillus anthracis* antigen. However, the Office action alleges that the use of oligodeoxynucleotides comprising SEQ ID NO: 200 are not enabled, because "the bases flanking the CpG motif confer part of the activity of the CpG oligonucleotide." The Office action appears to allege that any oligodeoxynucleotide that includes SEQ ID NO: 200 would not be effective in increasing the immunogenicity of a

vaccine against *Bacillus anthracis*. The only evidence provided in the Office action is a conclusory statement that this effect is "noted by the Applicant and widely recognized in the art." However, no specific statements by the Applicant are referenced in the Office action, and no scientific basis for these assertions is provided. This is not an appropriate standard. MPEP § 2164.04 states:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)... The language should focus those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by *making specific findings of fact, supported by the evidence,* and then drawing conclusions based on these findings of fact. [emphasis added]

In the present application, the Examiner has not provided any supported fact, scientific reference, experimental result or explicit teaching that supports the assertion that one of skill in the art could not make or use oligodeoxynucleotides comprising SEQ ID NO: 200 to increase the immunogenicity of a vaccine against *Bacillus anthracis*.

The Applicants respectfully submit that the claimed methods are fully enabled for oligodeoxynucleotides comprising SEQ ID NO: 200. This is supported by what is known in the art, the present specification, and the additional data of record.

MPEP § 2164.03 states:

> The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art....Accordingly, what is known in the art provides evidence as to the question of predictability.

As disclosed in the specification (see page 21), K oligodexoynucleotides (ODNs) include at least about 10 nucleotides and include a sequence represented by Formula I:

$$5'\ N_1N_2N_3T\text{-}CpG\text{-}WN_4N_5N_6\ 3'$$

wherein the central CpG motif is unmethylated, W is A or T, and N_1, N_2, N_3, N_4, N_5, and N_6 are any nucleotides. The specification further discloses that eliminating the CpG dinucleotide motif from the K ODN significantly reduces immune activation, and incorporating multiple CpGs in a single K ODN increases immune stimulation. It is also disclosed that K ODNs containing CpG motifs at the 5' end are the most stimulatory, although at least one base upstream of the CpG is required. It is disclosed that the most active K ODNs contain a thymidine immediately 5' from the CpG dinucleotide, and a TpT or a TpA in a position 3' from the CpG motif.

The prior art, such as U.S. Patent No. 6,194,388 (of record), describes K-type ODNs with a CpG motif. As disclosed in U.S. Patent No. 6,194,388: "In the course of these studies, it became clear that the bases flanking the CpG dinucleotide played an important role in determining the B cell activation induced by an ODN. The optimal stimulatory motif was determined to consist of a CpG flanked by two 5' purines (preferably a GpA dinucleotide) and two 3' pyrimidines (preferably a TpT or TpC dinucleotide)." U.S. Patent No. 6,194,388 also describes that ODNs of varying lengths are immunostimulatory. Specifically, U.S. Patent No. 6,194,388 discloses that an ODN comprising a CpG motif must be 8 nucleotides in length to be immunostimulatory.

Data is of record documenting that an ODN with the nucleic acid sequence set forth as SEQ ID NO: 200 increases the immunogeniciy of a vaccine against *Bacillus anthracis*. Any ODN comprising SEQ ID NO: 200 must have a CpG motif flanked by very specific sequences (such as a TpT dinucleotide 3' of the CpG motif). SEQ ID NO: 200 is the sequence TCGTCGTTTT GTCGTTTTGT CGTT. Thus, an ODN comprising the nucleotide SEQ set forth as SEQ ID NO: 200 is represented by Formula I, has multiple CpGs, includes one base upstream of the each CpG motif, contains a thmidine immediately 5' of a CpG dinucleotide, and a TpT in a position 3' from the CpG motif. These features must be present in any nucleotide comprising SEQ ID NO: 200, regardless of the length of the ODN.

The Office action alleges that the methods are not enabled because "bases flanking the CpG motif confer part of the activity of the CpG ODN." However, if an ODN includes SEQ ID NO: 200, then the bases flanking each CpG with the nucleotide sequence are set; *the bases flanking each CpG motif included in SEQ ID NO: 200 cannot be altered if the ODN includes the*

complete nucleotide sequence set forth as SEQ ID NO: 200. Thus, no variability of the bases flanking the CpG motifs exists in an oligodeoxynucleotide that comprises SEQ ID NO: 200.

As discussed above, the prior art also teaches that an ODN comprising a CpG motif must be at least 8 nucleotides in length to be immunostimulatory. However, any ODN comprising SEQ ID NO: 200 must be a minimum of 24 nucleotides in length (as SEQ ID NO: 200 is exactly 24 nucleotides in length). Thus, there also is no basis for any allegation that an olideoxynucleotide comprising SEQ ID NO: 200 would not be of a sufficient length to be immunostimulatory.

Klinman et al., *Expert Rev. Vaccines* 2: 305-315, 2003, copy submitted herewith as Exhibit A discloses that synthetic ODNs containing unmethylated CpG motifs act as vaccine adjuvants. Klinman et al. disclose that CpG ODNs affect antibody production and cytokine production, and note that increasing the number of CpG motifs can increase immunogenicity. Klinman et al. discloses that in humans the motif TCGTT is optimized for activity, while in mice the motif CAGTT is optimized for activity. Any nucleotide comprising SEQ ID NO: 200 must include three of these TCGTT motifs (see nucleotides 4-8 and 12-16 and 20-24). Klinman et al. discloses that these motifs stimulate the blood cells of humans and other primates. Klinman et al. conclude that the available evidence supports the conclusion that CpG motifs present in DNA vaccines serve an immunostimulatory function, and that the K-type ODNs can be used as immune adjuvants (see, for example, page 311-312). Thus, Klinman et al. provides further evidence that the TCGTT motifs present in any nucleotide comprising SEQ ID NO: 200 will function to enhance the immunogenicity of a vaccine against *Bacillus anthracis.*

There is no rational basis to assert that the methods of claims 69-77 are not enabled by the specification. The present specification, the experimental data of record, and the prior art, as well as post-filing date publications provide evidence any ODN comprising SEQ ID NO: 200 will be effective in the claimed methods.

In view of these remarks, reconsideration and withdrawal of the rejection as applied to claims 57 and 61-66, and as may be applied to new claims 69-77, are respectfully requested.

Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record, and that all of the pending claims are in condition for allowance. Withdrawal of the pending rejections and allowance of the claims is respectfully requested. If the rejection under 35 U.S.C. § 112, first paragraph is maintained, the Examiner and her supervisory are respectfully requested to contact the undersigned to arrange a telephonic interview prior to the issuance of any final Office action.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By _____
Susan Alpert Siegel, Ph.D.
Registration No. 43,121